Stem Cell Transplantation in Multiple Myeloma

STEM CELL TRANSPLANTATION IN MULTIPLE MYELOMA

Massimo Offidani,1Silvia Gentili,1 Francesca Gay,2 Elena Aghemo,2 Laura Maracci,1 Laura Corvatta,1 Antonio Palumbo2

1Clinica di Ematologia AOU Ospedali Riuniti di Ancona, Ancona, Italy
2 Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy.

Corresponding author: Antonio Palumbo, Division of Hematology, University of Torino, Via Genova 3, 10126 Torino, Italy. E-mail appalumbo@yahoo.com. Tel: +39 011 633 4260.

Abstract: High-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) remains the standard of care for patients younger than 65 years of age with multiple myeloma (MM). However, this therapeutic approach has undergone substantial advances in this last decade, mainly due to the introduction of new drugs such as thalidomide, lenalidomide and bortezomib. These new drugs, in different combinations, have shown to significantly increase response rates after induction therapy and ASCT. Moreover, the positive results obtained with these agents in consolidation and maintenance strategies after ASCT could support the concept of continuous therapy in the next future, whose ultimate goal is the long-term control of the disease and the improvement of outcome. Preliminary data from studies investigating next generation proteasome inhibitors, such as carfilzomib and ixazomib, used upfront as well as at subsequent therapeutic lines, demonstrate the possibility of achieving molecular remission in most of the patients. The deeper responses obtained with new drug-combinations questioned the role of ASCT, and large, ongoing, phase 3 trials will shed light on the role and the timing of ASCT.

INTRODUCTION

Despite a median age at diagnosis of 69 years, 38% of patients with multiple myeloma (MM) are less than 65 years old as reported by Recent Surveillance, Epidemiology, and End Results (SEER) data from the United States National Center for Health Statistics [1]. Between 2008-2012, MM was diagnosed in 3.7% of people aged less than 45 years, in 11.3% among people aged 45-54 years and among 23.2% in that aged 55-64 years. Starting in the late 1990s, the increased used of high-dose therapy (HDT) and better supportive care have prolonged long-term survival of patients younger than 60 years but a statistically significant improvement of survival, if compared with previous years, was seen only since 2000 due to the introduction of new drugs such as thalidomide, bortezomib and lenalidomide [2,3]. A retrospective analysis of 1538 patients with MM diagnosed between 1999 and 2008 showed a median overall survival (OS) of 93 months and 53 months in patients ≤ 45 years and > 45 years, respectively (p=0.001) [4].

A phase III trial in young patients demonstrated the superiority of HDT and autologous stem cell transplant (ASCT) over chemotherapy [5]. HDT significantly increased event-free survival (median EFS: 28 vs. 18 months; p = 0.01) and OS (median OS: 57 vs. 44 months; p = 0.03) if compared with chemotherapy. Subsequently, other five randomized trials compared HDT with chemotherapy [16-10] but a significant improvement in terms of EFS and OS was seen only in three of them[6-8]. Two studies [6, 7] and a meta-analysis of 10 randomized trials evaluating HDT versus chemotherapy reported a progression-free survival advantage (PFS) but not an OS benefit for HDT performed early in MM patients [11], thus questioning the role of up-front ASCT. However, the introduction of HDT as standard therapy has prolonged long-term OS, with 6-year OS not exceeding 50% in patients younger than 60 years treated in the 1990s [12].

Significant advances in the management of patients eligible for ASCT have been made with the introduction of novel drugs bortezomib, thalidomide and lenalidomide, with an increase in the depth of response. Indeed, a strong association exists between the degree of response and the outcome of patients [13]. These findings have led physicians to test new drug combinations both before and after ASCT, in order to enhance anti-myeloma activity.

This review provides an overview of the most recent therapeutic approaches in MM patients eligible for high-dose therapy and ASCT.

NEW INDUCTION REGIMENS BEFORE AUTOLOGOUS TRANSPLANTATION

The impact of thalidomide, in combination with dexamethasone or standard chemotherapy as induction therapy in preparation for ASCT was assessed in several trials. A retrospective case-matched study by Cavo et al [14] demonstrated the superiority of thalidomide plus dexamethasone (TD) over vincristine–doxorubicin–dexamethasone (VAD) regimen in term of overall response rate (ORR) [15]. These results were confirmed by a subsequent phase III trial [16], and another randomized study showed higher ORR and PFS with TD if compared with high-dose dexamethasone [17]. TD was also evaluated in combination with doxorubicin (TAD) [18] and cyclophosphamide (CTD) [19], both combinations induced a higher ORR if compared with VAD and cyclophosphamide-VAD (CVAD), respectively. Overall, thalidomide-based combinations were found to induce a complete remission CR rate not greater than 10%. Bortezomib in combination with dexamethasone (VD) was also compared with VAD in a phase III trial, showing a significant increase in response rates: the rate of at least very good partial response (VGPR) was 38% after VD induction and 54% after ASCT [20]. Similarly, better response

rates were obtained with the combination bortezomib-dexamethasone -doxorubicin (PAD) compared with VAD in a phase III trial [21]. Whereas long-term follow-up data of the combination bortezomib-dexamethasone-cyclophosphamide (Cybord; VCD) [22] led to at least a VGPR in 67% of patients after 4 cycles of therapy. The median PFS of the 63 patients enrolled, including 49 who underwent ASCT, was 40 months and the 5-year OS was 70% [22]. A recent published phase III trial aimed to demonstrate the non-inferiority of VCD (three 3-week cycles) compared with PAD (three 4-week cycles) in terms of response in 504 newly diagnosed MM patients. The at least VGPR was 37% in patients treated with VCD and 34.3% in those receiving PAD (p=0.58) [23]. In Table 1 we summarized the most important studies evaluating bortezomib in combination with chemotherapy as initial treatment in transplant-eligible patients. The addition of thalidomide to VD (VTD) compared with TD was evaluated in two large, prospective, randomized trials (Table 2). The GIMEMA trial [24, 25], enrolling 480 patients, compared three 3-week cycles of VTD versus TD, followed by double ASCT, and consolidation with two courses of VTD versus TD, and maintenance therapy with high-dose dexamethasone in both arms. VTD induction significantly increased CR rate (19% vs. 5%, p<0.0001) and ≥ VGPR rate (62% vs. 28%, p<0.0001) compared with TD. Response rates after first and second ASCT were also significantly higher with VTD than TD, and this translated in a longer PFS with VTD (57 months vs 42 months; p=0.001), respectively, after a median follow-up of 59 months. Remarkably, the advantage of VTD over TD was seen in high-risk cytogenetic patients defined by the presence of t(4;14) and/or del(17p), in whom the median PFS was 53 months as compared with. 24 months in those receiving TD, (p=0.0007) and the 4-year OS was 81% versus 66%, respectively (p=0.052) [24, 25]. Significantly higher response rates and longer PFS with VTD were reported also in a phase III trial comparing VTD vs TD vs VBMCP/VBAD/B (vincristine, BCNU, melphalan,

cyclophosphamide, prednisone/vincristine, BCNU, doxorubicin, dexamethasone/bortezomib). Yet VTD was not able to overcome the poor impact of high-risk cytogenetics [26, 27]. Another phase 3 study evaluated four 3-week VD cycles in comparison with four 3-week VTD with lower dose bortezomib (1 mg/m^2 instead of 1.3 mg/m^2) showing a significant higher response rate with VTD but no difference in terms of median PFS (26 months with VD and 30 months with VTD), after a median follow-up of 32 months [28]. A meta-analysis of four phase III trials comparing the efficacy and safety of bortezomib-based and nonbortezomib-based induction demonstrated a consistent benefit of bortezomib-based induction on response rates, PFS and OS [29]. As for the type of triplet combination to use as induction therapy, prospective randomized studies comparing PAD vs. VTD vs. VCD are lacking, although either VTD (recently approved by EMEA as induction in transplant-eligible patients) and VCD have shown to exert significant activity. A retrospective analysis evaluating response and safety for VTD and VCD induction administered in preparation for subsequent ASCT in two groups of patients matched for the main characteristics found that VTD was associated with higher CR rate (19% vs. 7%, $p<0.001$) and ≥ VGPR rate (62% vs. 39%, $p<0.001$). As expected, grade 3-4 hematologic toxicity was more frequent in the VCD arm (12% vs. 5%), by contrast grade 3-4 peripheral neuropathy was more common with VTD (7% vs. 2%) [30]. A phase III trial (IFM2013-04) compared four cycles of VTD vs. four cycles of VCD prior ASCT in 340 newly diagnosed MM patients. At least VGPR, the primary endpoint of study, was achieved by 66.3% of patients receiving VTD induction compared with 56.2% treated with VCD ($p = 0.05$) as well as PR rate in VTD arm resulted significantly higher than in VCD (92.3% vs.83.4%, $p=0.01$). Similarly to the abovementioned study, hematologic toxicity, was more frequent in VCD arm while peripheral neuropathy in VTD one [31].

In contrast with TD and VD, the combination lenalidomide plus dexamethasone (RD) has been not compared with the “old” standard chemotherapy as induction therapy before ASCT in newly diagnosed MM. However, a study including both young and elderly patients, compared lenalidomide plus high-dose dexamethasone (RD) versus plus low-dose dexamethasone (Rd); 96 patients underwent ASCT after 4 cycles of therapy and the 3-year OS was 94% in patients younger than 65 years [32, 33]. Based on preclinical findings showing the synergistic activity of bortezomib and lenalidomide [34], a phase I/II study [35] evaluated RD in combination with bortezomib (VRD): 66 patients received eight 3-week VRD cycles with or without ASCT after a minimum of 4 induction cycles. Best responses achieved by 28 patients before undergoing ASCT were CR/ near complete remission (nCR) 21%, at least VGPR 47%, at least partial response (PR) 90%. The activity of this combination was confirmed by a phase II study including 31 patients who received three VRD courses as induction, followed by ASCT, two VRD cycles as consolidation, and maintenance with lenalidomide for one year [36].

Carfilzomib is a second generation irreversible proteasome inhibitor that showed to be active when combined with lenalidomide and dexamethasone (KRd) in relapsed/refractory MM [37]. More recently, the positive results obtained in the relapsed setting, led to the evaluation of carfilzomib also in newly diagnosed MM. After a phase I/II study [38], a phase II study evaluated this regimen in transplant eligible patients [39]. Sixty-one patients (38% with high-risk cytogenetics) received 4 cycles of KRd as induction, HDT and ASCT, 4 cycles of KRd as consolidation post-ASCT and 10 cycles of KRd (with a modified schedule of carfilzomib) as maintenance, with lenalidomide alone after cycle 18. After induction, 85% of patients achieved at least a VGPR (8% stringent CR [sCR]) that further improved to 97% (22% sCR) after ASCT when 60% of patients were negative for minimal residual disease (MRD) assessed by flow cytometry. Main grade 3-4 side effects were

lymphopenia (25.8%), thrombocytopenia (11.3%) and thromboembolic events (8%). A similar combination but including thalidomide instead of lenalidomide (KTd) was investigated by the European Myeloma Network (EMN): 91 patients received 4 cycles of KTd as induction followed by ASCT and by 4 cycles of KTd as consolidation. The rates of at least VGPR after induction and ASCT were 68% and 76%, respectively and the 3-year PFS was 72% [40]. Ixazomib was the first oral proteasome inhibitor to be evaluated in MM [41, 42]. Two phase I/II studies in patients eligible and ineligible for ASCT evaluated Rd in association with ixazomib [43, 44]. In the first one [43], 65 patients, including 22 who underwent ASCT, received weekly ixazomib plus Rd; after 6 cycles of therapy, 90% achieved at least PR, 48% at least VGPR and 23% CR plus sCR; the main grade 3-4 toxicities were diarrhoea (17%), neutropenia (12%), thrombocytopenia (8%) and peripheral neuropathy (6%). Moreover, 88% of patients obtaining a CR and who could be evaluated for MRD by multiparameter flow cytometry, were confirmed to be MRD-negative. A second phase I/II study [44] evaluated the combination lenalidomide, dexamethasone plus ixazomib, given twice-weekly allowing ASCT until after 8 cycles. Ninety-five percent of patients achieved at least a PR, 71% at least a VGPR, 21% a CR plus sCR and the analysis of MRD by flow cytometry in patients with CR showed the achievement of MRD negativity in 82% of patients. One third of patients proceeded to ASCT and no adverse impact of induction therapy on stem cell mobilization was reported. Most common grade 3 side effects were rash (16%), pneumonia (6%) and peripheral neuropathy (5%) whereas no grade 4 toxicities were reported. A phase III trial comparing MLN9708 plus lenalidomide and dexamethasone with placebo plus lenalidomide and dexamethasone in newly diagnosed MM (NCT01850524) is ongoing. Finally, quadruplet combinations including a proteasome inhibitor with cyclophosphamide, dexamethasone and an immunomodulatory agent have been explored as induction in transplant-eligible patients (VDCR, CYKLONE) [45, 46] but no substantial advantages have been seen. Figure 1 reports high quality

response rates of the main triplet and quadruplet combinations investigated as induction in transplant-eligible patients.

Monoclonal antibodies (MoAbs) are emerging as very promising therapeutic strategies in the management of MM patients [47]. Elotuzumab, a humanized MoAb targeting CS1 (SLAMF7), and daratumumab, targeting CD38, have been recently approved by the US Food and Drug Administration (FDA) for the treatment of relapsed/refractory MM but several ongoing trials are evaluating the incorporations of these agents in backbone regimens for the treatment of transplant eligible patients. A phase II study (NCT02375555) is testing the combination of lenalidomide, bortezomib, dexamethasone and elotuzumab (E-VRD) as induction, with the option to ASCT after 4 cycles. Another phase III trial (CASSIOPEIA) (NCT02541383) is comparing 4 cycles of VTD induction vs. VTD plus daratumumab followed by ASCT.

The incorporation of new drugs as bortezomib into conditioning regimen [48] did not show to improve outcome compared with melphalan 200 mg/m^2, remaining now the established conditioning regimen for MM [49]. Moreover, a European Group for Blood and Marrow Transplantation (EBMT) phase III trial assessing the safety and efficacy of CD34+ selection compared to unselected PBPC in patients with MM undergoing ASCT after induction therapy with old drugs (vincristine, doxorubicin and dexamethasone), found no benefit for patients receiving CD34+ selected PBPC. Particularly, after a median follow-up of over 5 years, CD34+ selection did not reduce relapse risk after HDT and increased the risk of severe post-transplant infections [50].

THE ROLE OF AUTOLOGOUS TRANSPLANTATION IN THE ERA OF NEW DRUGS

The significant association between the depth of response before or after HDT/ASCT and long-term outcomes (time to progression [TTP] and OS) reported by a meta-analysis of 21 studies conducted until the early 2000s [51] has been confirmed by subsequent trials evaluating novel agent combinations as induction regimens. In the IFM 2005-01 trial comparing VD vs. VAD, [52] the achievement of VGPR or better after induction was a prognostic marker of better PFS. In the GIMEMA trial comparing VTD vs. TD, a multivariate analysis found that the achievement of CR or nCR after induction together with low β2-microglobulin, absence of t(4;14) with or without del (17p), randomization to receive VTD, was positively correlated with PFS [24]. A significant association was found also between quality of response post-transplant and both EFS and OS [13]. Consistently, a recent study demonstrated that patients receiving new drugs as induction and achieving a sCR after ASCT (24%) had a significant improvement in TTP and OS if compared with the patients achieving CR or nCR, highlighting the importance of reaching a deeper degree of response [53]. MRD by multiparameter flow cytometry is able to predict PFS in the transplant setting [54-56] and its prognostic value is independent of treatment type [57]. Moreover, MRD level as a continuous variable at day 100 after ASCT independently predicts PFS and OS with approximately 1 year median OS benefit per log depletion and, remarkably, this effect has been seen in patients achieving a conventional CR [58]. The increased frequency and extent of response obtained with the most recent novel agent combinations upfront led physicians to question the role of ASCT in young MM patients **(**Figure 1). In patients receiving KRd response rates after 8 cycles included at least VGPR in 91% of patients, nCR/CR/sCR in 73% and at least a CR in 42%, with limited severe toxicities. Moreover, all patients achieving at least a nCR assessed by multiparameter flow cytometry were MRD negative [59]. Although this is a phase II study with a short follow-up (12 months), the results are very encouraging and suggest the possibility of delaying

ASCT if deep response is achieved and maintained. Timing of ASCT is another major point under debate. Two retrospective studies found no statistically significant differences in PFS and OS between patients who received early and late ASCT [60, 61]. Moreover, in the phase II study evaluating the combination VRD in newly diagnosed MM with the possibility of receiving ASCT after completing four cycles of therapy, a post-hoc analysis detected no differences in PFS and OS, whether patients had received ASCT or not [35]. The first prospective randomized trial comparing the standard HDT followed by ASCT with the combination melphalan, prednisone and lenalidomide (MPR) has been conducted by Italian myeloma group [62]. All patients received four 28-day cycles of Rd as induction and subsequently were randomized to consolidation with six 28-day cycles of MPR or two 4-month high-dose melphalan (MEL200) plus ASCT. PFS was significantly longer in patients who received MEL200 (median PFS: 43 vs. 22.4 months, hazard ratio HR 0.44, $p<0.001$) and so was also OS (4-year OS: 81.6% vs. 65.3%, HR .55, $p=0.02$). The superiority of MEL200 over conventional chemotherapy plus lenalidomide was confirmed by two other phase III trials conducted by the EMN [63] and IFM/Dana-Farber Cancer Institute [64]. In the first study [63], patients received four 28-day cycles of Rd as induction and then randomized to receive consolidation with six 28-day cycles of cyclophosphamide, lenalidomide and dexamethasone (CRd) or MEL200-ASCT. After a median follow-up of 4 years patients who underwent ASCT had a significantly longer PFS (median PFS: 42 vs. 28 months, HR .67, $p=0.014$) and OS (4-year OS: 87% vs. 71%, HR .51, $p=0.028$) if compared with those receiving CRd. In the second trial [64], 700 patients were randomized to receive 3 induction cycles of VRD followed by ASCT and 2 cycles of VRD as consolidation or 8 cycles of VRD. After a median follow-up of 39 months, median PFS, the primary objective of the trial, was 34 months and 43 months in the VRD and transplantation arm respectively (HR=.69, $p<0.001$). The complete response rate was significantly higher in the transplant arm compared to VRD arm ((59% vs. 49%, $p=0.02$) as

well as superior was the rate of MRD negativity by FCM (80% vs. 65%, p=0.001). Another phase III trial (EMN-02) compared MEL200 plus ASCT with a consolidation consisting of four cycles of VMP enrolled 1500 patients as planned but the results are not available, yet..

Recently, a discussion concerning the presence of subgroups of patients not benefiting from ASCT is ongoing. A study with 855 patients who received bortezomib-based induction therapy followed by ASCT [65] identified a percentage of patients (8%) with high lactate dehydrogenase level, ISS3 and adverse cytogenetics defined by the presence of t(4;14) and/or del(17p), characterized by a 2-year OS of 52%. In a pooled analysis of two phase III trials in which patients, after Rd induction and stem cell mobilization, were randomized to either consolidation with two MEL200 and ASCT or 6 cycles of chemotherapy plus lenalidomide, MEL200 plus ASCT was found to not significantly improve PFS and OS in patients with ISS3, high-risk cytogenetics and in those not achieving at least a VGPR after induction [66]. Finally, a recent update of Total Therapy approaches reported a 5-year PFS of 71% and 25% in GEP70-defined low risk and high risk patients, respectively. Moreover, PFS, CR duration and TTP curves reached a plateau at ~ 5 years in high-risk MM as opposed to > 10 years in low-risk GEP70 patients, suggesting the need novel experimental treatments in high-risk patients [67].

STRATEGIES TO PREVENT RELAPSE AFTER TRANSPLANTATION

During the past decade, many advances have been made in the prognosis of patients with MM. Thanks to the use of ASCT and the introduction of the immunomodulatory drugs and the proteasome inhibitors, survival has increased over the past 20 years [68-70].

However, despite improvements in treatment options with intensive induction and tandem ASCT, most patients with MM ultimately relapse and die from resistant disease. Based on

the successful results seen with the incorporation of novel agents into induction therapy in preparation for ASCT, researchers are currently testing new drugs also as post-ASCT consolidation and maintenance therapy. The aim of all these therapeutic strategies is to prevent relapse and control disease with the long-term goal of MRD negativity, keeping patients disease-free.

Consolidation therapy

Consolidation is a short distinct course of treatment (usually 2 or 4 cycles) with a powerful combination of drugs and is used to further improve the responses attained before initiation of maintenance therapy.

In one of the first trial in the ASCT setting, 4 cycles of VTD consolidation were given to 39 bortezomib-naïve patients who had achieved at least a VGPR after tandem ASCT [71]. This approach significantly improved CR from 15% to 49% and molecular remissions from 3% to 18% [72]. In an Italian phase III study, patients were randomized before and after double ASCT to receive VTD or VT as induction and as consolidation therapy [73]. Two cycles of VTD and TD increased the CR rate from 49% to 61% and from 40 to 47%, respectively. Although results suggested a benefit of the 3-drug combination over the 2-drug combination in terms of PFS (3-year PFS: 60% vs. 48% respectively; p=0.042), this advantage was not seen in OS. Similar results were observed with VTD consolidation compared with control group in a retrospective analysis [74]. Despite a higher CR rate (52% with consolidation vs. 30% without consolidation treatment; p=0.001) and longer TTP in the interventional group (not reached vs. 25 months), OS was not different between two groups. In the Nordic Myeloma Study Group trial [75], patients treated with 20 doses of single agent bortezomib consolidation after ASCT obtained a better quality of response compared with patients receiving placebo (≥VGPR: 71% vs. 57%; p=0.001) and longer PFS (median PFS: 27 vs. 20 months; p=0.05) but not an improved OS. Notably, all

patients had never been treated with proteasome inhibitors before consolidation and only patients who failed to achieve at least a VGPR after ASCT benefited from bortezomib consolidation. The combined results of 2 phase III studies (MMY3012 and MMY3013) showed comparable results [76]. Patients (N = 380) were randomized to receive 16 weekly doses of bortezomib or no therapy after various induction regimens (50% containing bortezomib) followed by transplant. The probability of achieving at least a VGPR was higher in the bortezomib group (62%) than in the control group (48%) and this improvement led to a 6-month gain in PFS (median PFS: 34 vs. 28 months; p=0.0058). There was no difference in OS between the groups. In the IFM 2005-02 study [77], all patients enrolled (N = 614) were treated with lenalidomide consolidation (25 mg for 21 days) following ASCT, and then randomized to lenalidomide or placebo maintenance. The at least VGPR rate improved from 58% after ASCT to 69% after 2 cycles of lenalidomide consolidation. Two cycles of VRD have been adopted as consolidation after the same induction regimen and single ASCT in the phase II IFM study (IFM 2008) [36]. This approach increased the rate of VGPR + CR, including sCR, from 70% after ASCT to 87% after consolidation.

Based on impressive results obtained in induction therapy, several trials are investigating carfilzomib combined with immunomodulators and dexamethasone as consolidation. In a multicenter phase II study, the higher CR rate improved from 33% after ASCT to 63% after 4 cycles of KTd consolidation. No toxicity-related treatment discontinuation was observed during consolidation [40]. Preliminary results with lenalidomide instead of thalidomide as consolidation are quite impressive. In a recent study, the rate of sCR increased significantly from 29% after transplant to 72% with KRd consolidation, including 88% of patients achieving MRD negativity [78].

Based on the current data, consolidation theray seems to have a positive impact on clinical outcome of MM patients. However these data require confirmation in prospective trials,

which might also clarify the optimal consolidation regimen. Until then, consolidation is not recommended outside clinical trials [79, 80].

Maintenance therapy

Maintenance strategy involves the use of a single or at most two agents with minimal toxicity, generally given for a prolonged period of time. The goal of continuous therapy is to maintain or even improve treatment response after induction, and ultimately prolong remission and improve OS.

The role of maintenance in the transplant setting has been investigated in several trails with agents such as interferon-α, glucocorticoids and melphalan. However, these drugs failed to show significant benefits in outcomes and manageable toxicity profiles [81-84].

Different results have been obtained with novel agents.

Continuous thalidomide until progression after ASCT has been evaluated in four trials [18, 85-88]. Although these studies all reported a longer EFS or PFS in patients receiving maintenance, only in the French IFM-99 study this translated into a survival advantage (4-year OS: 87% vs. 75%, $p<0.04$) [85]. Of note, unfavourable results have been obtained in the subset of patients with high-risk cytogenetics. The MRC Myeloma IX trials found that the OS was considerably worse for patients with t(4;14), t(14;16), t(14;20), gain(1q) or del(17p), randomized to thalidomide, as opposed to placebo maintenance (35 vs. 47 months, $p=0.01$) [87, 88].

Four other phase III trials assessed the role of thalidomide in combination with steroids as maintenance therapy after ASCT [89-92]. As previously seen, three studies reported a better PFS, which did not translated into an OS benefit [90-92]. In the study published by Stewart et al [92], patients receiving thalidomide and prednisone had a significant worsening in their quality of life compared with those who did not receive maintenance.

Although thalidomide is administered orally and has no hematological toxicity, the prolonged exposure to thalidomide was not well tolerated. Grade 3-4 peripheral neuropathy (PN) was the major concern, leading to early treatment discontinuation in a significant number of patients. Other important adverse events frequently associated with thalidomide were constipation, sedation and increased risk of venous thromboembolism (VTE). Taken together, all these data suggest that thalidomide is not the ideal candidate for a prolonged administration.

More promising data have been obtained using lenalidomide, a derivative of thalidomide, that is less toxic and more active than its parent drug. Lenalidomide maintenance versus no maintenance has been investigated in three randomized trials in transplant-eligible patients [77, 93, 94]. The CALGB-100104 trial enrolled 462 patients after single ASCT [93]. An updated analysis of this phase III study was recently reported and confirmed a relevant benefit with lenalidomide continuous therapy [95]. After a median follow-up of 65 months, patients receiving lenalidomide maintenance until progression had a longer TTP compared with those in the placebo arm (median TTP: 53 vs. 27 months, $p<0.001$) and a better OS (median OS: not reached vs. 76 months, $p=0.001$). Treatment was equally effective, regardless of the achievement of CR at randomization or previous exposure to immunomodulatory drugs during induction. In the IFM 2005-02 study [77], lenalidomide maintenance significantly improved PFS compared with placebo (median PFS: 41 vs. 23 months, $p<0.0001$). However the 5-year OS was 68% in the lenalidomide group and 67% in the observation group (HR 1) and the survival after first progression was shorter in the lenalidomide arm when compared with placebo (median OS: 29 vs. 48 months, $p<0.0001$) [96]. Unlike the CALGB-100104 study, in this trial patients did not receive immunomodulatory drugs during induction, 21% of patients had a double transplant and a pre-ASCT or post-ASCT consolidation was allowed. Duration of maintenance was different between the two trials. Due to concerns regarding a higher incidence of secondary primary

malignancies (SPMs) in the lenalidomide arm, in the IFM study lenalidomide was given for a fixed duration (median time of 2 years), while in the CALGB study lenalidomide administration was prolonged until progression. Although in the CALGB trial an increased risk of developing a SPM in the lenalidomide group was also reported (p=0.005), the cumulative incidence risk of progression (p <0.001) or death (p <0.001) was superior for the placebo group [93, 95].

In the third study, 402 MM patients were randomized to lenalidomide maintenance or no maintenance after chemotherapy or double ASCT [94]. In a landmark analysis both median PFS and OS from the start of maintenance were significantly superior with lenalidomide compared with the control group (PFS: 42.7 vs. 17.5 months, p<0.0001; 4-year OS: 80% vs. 62%, p=0.01), with a median follow-up of 48 months.

Another Italian phase III study [97] reported encouraging data using the same 2x2 design, and compared conventional CRd with tandem ASCT, and in the second part of the trial, lenalidomide plus prednisone maintenance versus lenalidomide alone. After a median follow-up of 31 months, the 3-year PFS was 60% for patients receiving lenalidomide plus steroid versus 38% for patients treated with lenalidomide alone (p=0.003), whereas OS was comparable between the two arms.

Lenalidomide could be the ideal drug for prolonged use because of the oral administration and its safety profile, nevertheless the three trials mentioned above found a 2- to 3-fold increase in the risk of SPMs with lenalidomide maintenance [77, 93, 94]. A recent meta-analysis [98] of seven randomized trials confirmed a higher incidence of SPMs in patients receiving lenalidomide when combined with melphalan. On the contrary, lenalidomide plus other agents such as steroids or cyclophosphamide, did not increase the risk of SPMs. So far, the benefits of lenalidomide maintenance do outweigh the increased risk of SPM, but patients should be carefully evaluated for SPMs before and during lenalidomide treatment.

The optimal duration of lenalidomide maintenance is still under debate. Based on the increased risk of SPMs, a fixed duration of 2 years was proposed for lenalidomide maintenance [99]. However a retrospective analysis [100] has recently shown that patients treated with prolonged lenalidomide (> 2 years) have a longer OS compared with those who stopped therapy (HR 0.36, 95% CI 0.19-0.67, p = .0015), whereas the risk of developing an SPM was not associated with the duration of maintenance treatment.

Two phase III trials have investigated the role of bortezomib after ASCT, demonstrating a substantial PFS benefit with this drug, while OS was improved in only one study [21, 26]. In the study conducted by Sonneveld et al [21], PAD followed by post-ASCT bortezomib maintenance for 2 years was associated with a significant PFS and OS benefit compared with VAD induction and post-ASCT maintenance with thalidomide. Bortezomib-based therapy was able to overcome the poor prognosis conferred by deletions of chromosome 17p or renal impairment, which continued to have an adverse prognostic impact in the VAD/thalidomide arm. One limit of this trial is its design, as it makes hard to determin whether the benefit is due to induction or maintenance or both. A landmark analysis form the start of maintenance revealed a better OS for the bortezomib arm (HR 0.71, p= .035) compared with thalidomide maintenance, while no statistically significant difference in terms of PFS was noted in the two arms [101].

In the PETHEMA/GEM trial [26], patients who received VT maintenance had a longer PFS than those who received thalidomide or interferon (2-year PFS: 78% vs. 63% vs. 49%, p=0.01), while OS were comparable. As for the toxicity of the two drugs, bortezomib induces a lower rate of PN than thalidomide and it is not associated with an increased risk of SPM. However bortezomib has the disadvantage of the intravenous administration.

MLN9708 (Ixazomib) is the next-generation proteasome inhibitor, the first orally available proteasome inhibitor used in clinical trials and it is currently under investigation as maintenance treatment. In a phase II study, 21 patients received weekly ixazomib

maintenance therapy after 9 cycles of induction with ixazomib-lenalidomide-dexamethasone [102]. After a median follow-up of 16.9 months from start of maintenance, 33% of patients improved their response and no serious adverse events related to treatment were observed during maintenance.

Based on the results of lenalidomide maintenance post-ASCT, several agents have been evaluated in combination with lenalidomide to further improve quality of response and outcome, without excessive toxicity. Shah et al. evaluated the combination of ixazomib with lenalidomide as maintenance therapy post ASCT in 16 patients [103]. Preliminary data of this phase II study indicated a manageable safety profile. Only one patient discontinued treatment due to side effects (pneumonia) and six (30%) required a dose reduction of ixazomib or lenalidomide. Grade 3-4 non-hematologic toxicity was limited to grade 3 rash in one patient whereas most common hematologic adverse events were neutropenia and thrombocytopenia occurring in 35% and 15% of patients, respectively.

A phase I dose-escalation trial [104] has recently tested maintenance with lenalidomide plus vorinostat, a nonspecific oral histone deacetylase inhibitor. Fifteen patients were included, and preliminary results indicated a not negligible toxicity. Almost all patients experienced grade 3-4 adverse events, primarily hematologic. The rate of discontinuation for toxicity of 33% suggests that vorinostat may not be the ideal agent to combine with lenalidomide as maintenance, unless a substantial survival benefit will be reported. Interesting results were also seen when bortezomib was given with lenalidomide-dexamethasone for 3 years in two US trials [105, 106]. In both studies this strategy was effective in patients with high-risk cytogenetics for instance in patients carrying 17p deletion. However it is not clear which agent or which part of therapeutic approach contributed to achieve these results. In the Arkansas trial [105] bortezomib was used in induction, consolidation and maintenance phases, confirming the results obtained with bortezomib-based treatment in patients with adverse cytogenetics; whereas data

published by Nooka et al. indicated that a long-term administration of multi-drug combination could be the key to longer survival [106].

Although maintenance therapy seems to positively impact on the prognosis of patients with MM, many questions regarding the choice of drug or combination of drugs, as well as the optimal duration of treatment, are still unresolved. A wide variety of agents or combination of agents are currently under evaluation in clinical trials to address these questions (Table 3). To date, no specific guidelines are available and the risk-benefit ratio for each single patient should be carefully evaluated before starting maintenance therapy [79, 80].

AUTOLOGOUS TRANSPLANTATION IN ELDERLY PATIENTS

Despite the introduction of novel agents, the improvement in survival was mainly seen in younger patients, whereas it was modest or absent in the elderly or very elderly patients [69, 70, 107]. Age is historically a powerful predictor of survival in MM, this has also been confirmed by recent data. A meta-analysis of 1435 elderly patients enrolled in 4 randomized trials who received treatment with thalidomide and/or bortezomib, showed that elderly patients still had inferior OS as compared with younger subjects (3-year OS 57% for patients younger than 75 years vs. 68% for those older than 75 years; $p<0.001$) [108]. Despite several trials have recently reported impressive and unprecedented CR rates and PFS times, they did not always translate into a survival benefit.

The survival improvement observed in the last few years in younger patients seems to be associated with the introduction of ASCT and, as previously discussed, ASCT remains the gold standard for transplant-eligible. Patients older than 65 years of age are generally considered ineligible for ASCT but today the age cut-off of 65 years is no longer valid [109]. Several studies have retrospectively evaluated the role of ASCT in elderly patients, suggesting that ASCT should be offered more frequently to these patients [110- 117]. Most

of these trials have been performed in the US, where the National Comprehensive Cancer Network (NCCN) guidelines for MM do not limit this procedure based on the patient's age. An analysis conducted using data from the US and Canada [118] demonstrated that an increasing number of older patients with newly diagnosed MM underwent ASCT, especially in recent years. According to that analysis, ASCT seems to be complementary to novel agents in all age categories, suggesting that transplant may even be proposed to elderly patients, if clinically indicated. These findings have been recently validated in an analysis including 11430 patients receiving ASCT between 2008 and 2011 [119]. Patients older than 70 years of age reported rates of relapse, not-relapse mortality, and PFS similar to those observed in patients 60 to 69 years of age and those under 59 years. As expected, a lower survival was seen in elderly patients.

However few prospective trials have examined the potential role of ASCT in patients aged >65 years. An Italian study demonstrated the feasibility of melphalan 100 mg/m2 (MEL 100) in patients older than 65 years [120]. The Italian group subsequently showed in a randomized trial that patients aged 65-70 years receiving two or three courses of MEL 100 with ASCT had better outcome compared with those treated with chemotherapy (3-year EFS: 31% vs. 18%, p=0.01; 3-year OS: 73% vs. 58%) [7]. When patients ≥70 years received MEL 200 followed by ASCT an unacceptable transplantation-related mortality (16%) was noted by Badros et al [121]. A consequent reduction in the dosage of melphalan to 140 mg/m2 was applied and showed to be more safe in this subset of patients. Yet, the French group found no advantage with ASCT in elderly patients. In the French study [122], which included patients age 65 to 75 years, PFS was superior in patients treated with MPT compared with those randomized to MEL 100 (HR 0.54, p=0.0002), and the OS was longer (HR 0.69, p=0.027).

Notably, all patients enrolled in these studies received only conventional chemotherapy before ASCT. The complementary role of new drugs and transplant in elderly MM patients

was investigated in a phase II trial in which patients aged 65-75 years received bortezomib-based induction (PAD regimen), tandem MEL100, four cycles of lenalidomide-prednisone consolidation and lenalidomide maintenance [123]. After a median follow-up of 66 months, the median PFS was 48 months, while the median OS was not reached (5-year OS: 63%) and the 1-year OS rate was 92% [124]. However the risk of death due to adverse events was increased in patients older than 70 years than in younger patients (19% vs. 5%, p=0.024).

In conclusion, fit elderly patients with MM may benefit from either reduced-intensity ASCT or continuous therapy, both including novel agents. Yet, direct comparisons between these two approaches are still lacking. According to International Myeloma Working Group (IMWG), ASCT should be considered in very fit elderly patients [125]. Age can no longer be considered the only criterion to choose treatment in patients older than 65 years, but also psychological status, social support, performance status, and comorbidity should be taken into account, thus allowing physicians to provide the most appropriate personalized therapy [126, 127].

CONCLUSION

Although MM is typical of advanced age, more than one third of patients are younger than 65 years, and ASCT remains the standard of therapy in these patients. Yet, fit, elderly subjects showed to benefit from reduced intensity ASCT.

Significant survival improvements have been obtained in the last ten years with the incorporation of novel effective agents, such as thalidomide, lenalidomide and bortezomib in the transplant regimens. Bortezomib-based combinations as induction therapy increased response rate, PFS and OS. Next-generation proteasome inhibitors such as carfilzomib in combination with immunomodulatory agents induce very deep responses, with a high number of patients achieving MRD-negativity by flow cytometry. Consolidation

after ASCT has been shown to prolong PFS but it is not entirely clear whether this translates into a longer survival. Maintenance therapies with bortezomib and lenalidomide could be effective strategies, but there are some open questions regarding the duration and the tolerability of treatment. Moreover, it is still unknown whether a therapeutic strategy including consolidation and maintenance may be used in all patients or only in subgroups of patients namely those with high-risk features. The results obtained from the ongoing studies will clarify these questions. Finally, considering the high quality responses obtained with new drugs and the future availability of next-generation proteasome inhibitors, newer immunomodulatory agents and other classes of drugs such as antibodies, many steps forward will be made in the treatment of MM, and the role of ASCT may also be revised.

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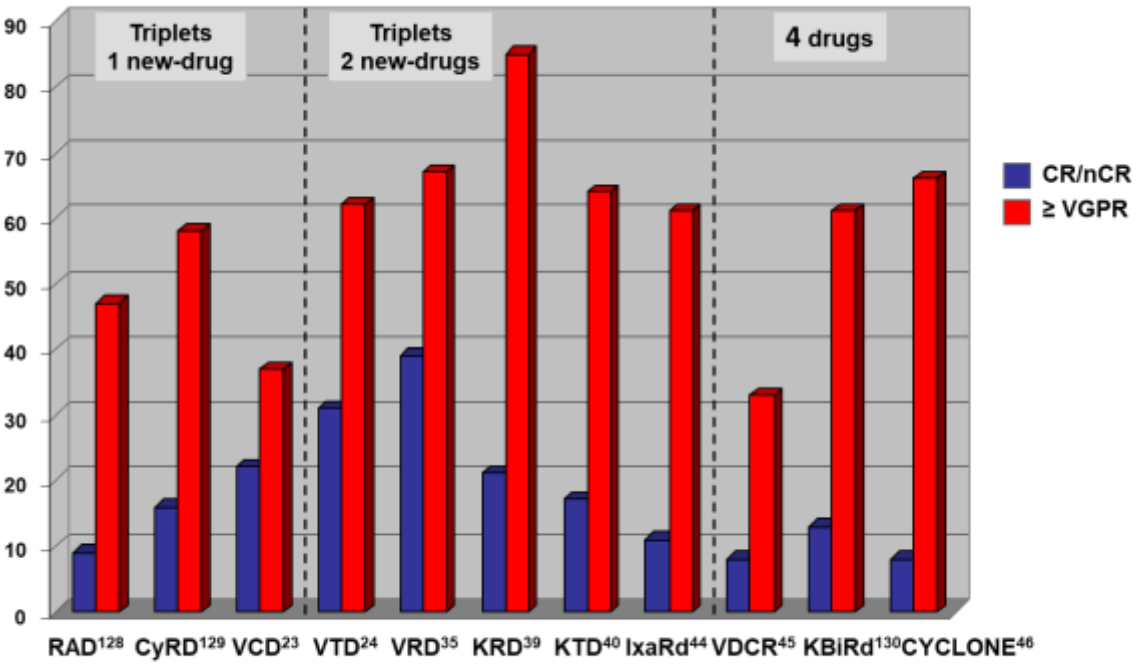
Figure 1 High-quality response rates assessed after 3-4 cycles of main triplet and quadruplet combinations evaluated as induction in transplant-eligible patients



RAD: lenalidomide, adriamycin and dexamethasone; CyRD: cyclophosphamide, lenalidomide, dexamethasone; VCD: bortezomib, cyclophosphamide, dexamethasone; VTD: bortezomib, thalidomide, dexamethasone; VRD: bortezomib, lenalidomide, dexamethasone; KRD: carfilzomib, lenalidomide, dexamethasone; KTD: carfilzomib, thaalidomide, dexamethasone; IxaRd: ixazomib, lenalidomide, dexamethasone; VDCR: bortezpmib, cyclophosphamide, lenalidomide, dexamethasone; KBiRd: carfilzomib, clarithromycin, lenalidomide, dexamethasone; CYKLONE: carfilzomib, cyclophosphamide, lenalidomide, dexamethasone